REMARKS/ARGUMENTS

Upon entry of this amendment, claims 1-13, 15-17, 19-21, 23-63, 65, 68-72, and 74 are pending in this application and are presented for examination. Claims 14, 18, 22, 64, 66, 67, and 73 have been canceled without prejudice. Claims 1, 5, 7, 8, 15, 19, 20, 23, 30-32, 42, 50-55, 61-63, 65, 71, 72, and 74 have been amended. No new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

I. FORMALITIES

The specification has been amended to correct several informalities. In particular, a typographical error with respect to the "Poynard et al." reference has been corrected on page 103 and in Table 8 on page 104. Further, typographical errors with respect to the numerical values in Table 8 on page 104 have also been corrected. These are obvious errors that a skilled person would readily recognize as such. Thus, no new matter has been introduced. Applicants respectfully request that the amendments to the specification be entered.

The heading of the abstract has been amended to read as "Abstract of the Disclosure." Thus, no new matter has been introduced. As such, Applicants respectfully request that the amendment to the abstract be entered.

Claims 1, 5, 7, 8, 15, 19, 20, 23, 30-32, 42, 50-55, 61-63, 65, 71, 72, and 74 have been amended. Claims 7, 8, 15, 19, 20, 23, and 74 have been amended to establish proper claim dependency. Support for amended claims 1, 5, 30-32, 42, 50-55, 61-63, 65, 71, and 72 is found throughout the specification as filed. In particular, support for amended claims 1 and 32 is found, for example, on page 4, line 6. Support for amended claim 5 is found, for example, on page 7, line 13. Support for amended claims 30, 31, 42, 50-53, 61, and 71 is found, for example, on page 15, lines 28-31. Additional support for amended claim 42 is found, for example, on page 36, lines 24-27. Additional support for amended claims 50-53 is found, for example, from page 39, line 27 to page 43, line 7. Support for amended claims 54, 55, 62, and 63 is found, for example, in Table 6 on page 93. Support for amended claim 65 is found, for example, from page 37, line 1 to page 43, line 7, and in Table 7 on pages 97-98. Support for amended claim 72 is found, for example, from page 37, line 1 to page 43, line 7, and in Example II on pages 95-105.

Thus, no new matter has been introduced. As such, Applicants respectfully request that the amendments to the claims be entered.

II. CLAIM OBJECTION

In the Office Action, the Examiner indicated that claims 1 and 32 were objected to because the abbreviation for α2-macroglobulin was not included in step (a). Applicants have amended claims 1 and 32 by adding the abbreviation for α2-macroglobulin to step (a). As such, Applicants respectfully request that the objection be withdrawn.

III. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 7, 31, and 42-74 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that claim 7 is self-dependent. In response, Applicants have amended claim 7 to establish proper dependency from claim 6.

The Examiner also alleges that the terms "no or mild liver fibrosis" and "moderate to severe liver fibrosis" in claims 31, 42, 50-53, 61, and 71 are relative terms. In order to expedite prosecution of the present case, Applicants have amended the claims to delete these terms and replace them with "F0-F1 fibrosis" and "F2-F4 fibrosis," respectively, which correspond to defined stages in the Metavir scoring system (page 16, line 25 to page 17, line 3).

Further, the Examiner alleges that the term "remaining individuals" in claim 42 is unclear. In response, Applicants have amended claim 42 to delete the term and replace it with "said individual." Likewise, claims 50-54 and 62 have been amended to refer to "said individual" instead of "a population of individuals."

Moreover, the Examiner alleges that the term "desired performance characteristic" in claims 65 and 72 is unclear. In order to expedite prosecution, Applicants have amended the claims to delete the term and recite that the cut-off values are independently selected to achieve an optimized clinical parameter selected from the group consisting of sensitivity, specificity, negative predictive value, positive predictive value, and accuracy.

The Examiner also alleges that claims 72 and 73 are unclear because they recite two cut-off values for each marker without defining which of them is used to determine whether the individual is positive or negative for the marker. In order to expedite prosecution, Applicants have amended claim 72 to recite that the individual is positive for the marker if its level is above both cut-off values. As claim 73 has been canceled, the rejection is rendered moot with respect to the claim.

In view of the above amendments to the claims, Applicants respectfully request that the Examiner withdraw all the 35 U.S.C. § 112, second paragraph rejections.

IV. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

A. Written Description Rejection

Claims 14, 18, 22, 54-64, and 65-74 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled the art that Applicants, at the time the application was filed, had possession of the claimed invention. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that Applicants have not adequately described the genus of specific binding agents that bind to α2-MG, HA, or TIMP-1. In order to expedite prosecution, Applicants have canceled claims 14, 18, and 22, thereby rendering the rejection moot with respect to these claims.

The Examiner also alleges that Applicants were not in possession of the assay method recited in claims 54-64 because Applicants have failed to demonstrate any combination of fibrotic markers where the use of a single cut-off value for each marker provides an accuracy of at least 90%. In order to expedite prosecution, Applicants have amended claim 54 to recite the use of at least two specific fibrotic markers, *i.e.*, ***α2-MG and HA***, wherein the cut-off value for each marker is independently selected such that, in a population having up to 60% liver fibrosis prevalence, the accuracy of diagnosing the presence or severity of liver fibrosis in the individual is ***at least about 70%***. In particular, entry 14 in Table 6 on page 93 of the instant specification shows that the combination of ***α2-MG and HA*** provides an accuracy of 79.90% in a

population having 59.3% liver fibrosis prevalence where a single cut-off value for each marker is used. Likewise, entries 10-13 and 15-17 in Table 6 show that the combination of α2-MG and HA with one or more additional fibrotic markers provides an accuracy of from 68.56% to 80.41% in a population having 59.3% liver fibrosis prevalence where a single cut-off value for each marker is used. As such, Applicants submit the instant specification adequately demonstrates that α2-MG and HA, together or in combination with one or more additional fibrotic markers, provide an accuracy of at least about 70% in a population having up to 60% liver fibrosis prevalence where a single cut-off value for each marker is used.

Further, the Examiner alleges that Applicants were not in possession of the genus of diagnostic assays encompassed by claims 65-74 because the claims fail to define the desired performance characteristics and one cannot envision which assays are within the genus of claimed diagnostic assays. As described above, Applicants have amended claims 65 and 72 to delete the term "desired performance characteristic" and recite that the cut-off values are independently selected to achieve an optimized clinical parameter selected from the group consisting of sensitivity, specificity, negative predictive value, positive predictive value, and accuracy. Applicants have also amended claims 65 and 72 to recite the use of at least three specific fibrotic markers, *i.e.*, ***α2-MG, HA, and TIMP-1***, wherein each marker either has one cut-off value (claim 65) or two cut-off values (claim 72), and the markers are independently selected to achieve an optimized clinical parameter. In this regard, Table 7 of the instant specification shows that different sets of cut-off values in which each marker has one cut-off value (*i.e.*, X1, Y1, and Z1) can be used to achieve optimization of sensitivity to rule out liver fibrosis or optimization of specificity to rule in liver fibrosis (pages 97-98). Further, Table 7 shows that a set of cut-off values in which each marker has two cut-off values (*i.e.*, X1, X2, Y1, Y2, Z1, and Z2) can be used to achieve optimization of clinical parameters such as specificity, negative predictive value, positive predictive value, and accuracy (page 101). Moreover, the instant specification discloses that one skilled in the art can use methods such as factorial design optimization to select appropriate cut-off values for each fibrotic marker to achieve optimized clinical parameters (page 37, line 1 to page 38, line 4). As such, Applicants submit the instant

specification adequately demonstrates that cut-off values for α2-MG, HA, and TIMP-1 can be used to achieve optimized clinical parameters such as those described above.

In view of the above amendments to the claims, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection.

B. Enablement Rejection

Claims 65-74 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that the term "desired performance characteristic" in claims 65 and 72 is not defined. As described above, Applicants have amended claims 65 and 72 to delete the term and recite that the cut-off values are independently selected to achieve an optimized clinical parameter selected from the group consisting of sensitivity, specificity, negative predictive value, positive predictive value, and accuracy. As such, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection.

V. REJECTION UNDER 35 U.S.C. § 102

Claims 65, 66, and 68-71 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Afdhal *et al.*, *J. Hepatol.* 27:993-1002 (1997). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that Afdhal *et al.* disclose a combination of two urinary markers, desmosine (DES) and hydroxylysylpyridinoline (HP), which provides an accuracy of over 80% for diagnosing liver fibrosis. The Examiner also alleges that Afdhal *et al.* disclose a combination of DES and HP with a third marker, the N-terminal propeptide of type III procollagen (PIIINP), which provides an accuracy of 84% for diagnosing liver fibrosis. In response, Applicants assert that Afdhal *et al.* do not teach or suggest the use of the specific combination of markers recited in amended claim 65. In particular, Afdhal *et al.* teach that DES, HP, and PIIINP are potentially useful markers for diagnosing liver fibrosis (page 993,

"Conclusions" section of abstract), but simply fail to teach or suggest the ***combined use of α2-MG, HA, and TIMP-1*** as is presently claimed for diagnosing the presence or severity of liver fibrosis as set forth in amended claim 65. As such, each and every element as set forth in amended claim 65 is not found in Afdhal *et al.* In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 102(b) rejection.

Claims 65 and 71 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Murawaki *et al.*, *J. Gastroenterol.* 36:399-406 (2001). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that Murawaki *et al.* disclose a combination of fibrotic serum markers, HA and matrix metalloproteinase-2 (MMP-2), for staging liver fibrosis. The Examiner also alleges that Murawaki *et al.* disclose a combination of HA and the 7S fragment of type IV collagen (PIVNP) for staging liver fibrosis. In response, Applicants assert that Murawaki *et al.* do not teach or suggest the use of the specific combination of markers recited in amended claim 65. In particular, Murawaki *et al.* teach that HA, MMP-2, and PIVNP are useful markers for staging or grading liver fibrosis (page 399, "Results" section of abstract), but simply fail to teach or suggest the ***combined use of α2-MG, HA, and TIMP-1*** as is presently claimed for diagnosing the presence or severity of liver fibrosis as set forth in amended claim 65. As such, each and every element as set forth in amended claim 65 is not found in Murawaki *et al.* In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 102(a) rejection.

Claims 65 and 71 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Walsh *et al.*, *J. Hepatol.* 32:325-330 (2000). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that Walsh *et al.* disclose a correlation between the type of liver fibrosis and the level of serum type IV collagen and laminin. In response, Applicants assert that Walsh *et al.* do not teach or suggest the use of the specific combination of markers recited in amended claim 65. In particular, Walsh *et al.* teach that type IV collagen and laminin are accurate non-invasive markers of liver fibrosis (page 325, "Conclusions" section of abstract), but simply fail to teach or suggest the ***combined use of α2-MG, HA, and TIMP-1*** as is presently

claimed for diagnosing the presence or severity of liver fibrosis as set forth in amended claim 65. As such, each and every element as set forth in amended claim 65 is not found in Walsh *et al.* In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 102(b) rejection.

Claims 65, 66, 69, and 71 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Xuhuai *et al.*, *Chin. Med. J.* 110:198-201 (1997). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that Xuhuai *et al.* disclose the combined use of type IV and VI collagen levels and other markers for diagnosing liver fibrosis. In response, Applicants assert that Xuhuai *et al.* do not teach or suggest the use of the specific combination of markers recited in amended claim 65. In particular, Xuhuai *et al.* teach that type IV and VI collagen are useful markers for diagnosing liver fibrosis (page 198, "Conclusions" section of abstract), but simply fail to teach or suggest the ***combined use of α2-MG, HA, and TIMP-1*** as is presently claimed for diagnosing the presence or severity of liver fibrosis as set forth in amended claim 65. As such, each and every element as set forth in amended claim 65 is not found in Xuhuai *et al.* In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 102(b) rejection.

Claims 65, 66, 68, 69, and 71 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Imbert-Bismut *et al.*, *Lancet* 357:1069-1075 (2001). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that Imbert-Bismut *et al.* disclose the diagnosis and staging of liver fibrosis with panels containing 5 or 6 markers. In response, Applicants assert that Imbert-Bismut *et al.* do not teach or suggest the use of the specific combination of markers recited in amended claim 65. In particular, Imbert-Bismut *et al.* teach that α2-MG, α2-globulin, gamma globulin, apolipoprotein A1, gamma glutamyltranspeptidase, and total bilirubin are the most informative markers for diagnosing liver fibrosis (page 1069, "Findings" section of abstract), but simply fail to teach or suggest the ***combined use of α2-MG, HA, and TIMP-1*** as is presently claimed for diagnosing the presence or severity of liver fibrosis as set forth in amended

claim 65. As such, each and every element as set forth in amended claim 65 is not found in Imbert-Bismut *et al.* In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 102(a) rejection.

VI. REJECTION UNDER 35 U.S.C. § 103(a)

Claims 54, 55, and 57-64 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Imbert-Bismut *et al.*, *Lancet* 357:1069-1075 (2001). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

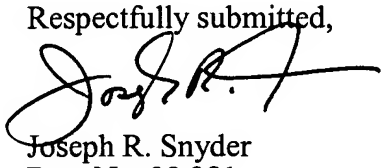
The Examiner alleges that one skilled in the art who repeated the analysis of the 5 or 6 marker panels taught by Imbert-Bismut *et al.* upon a different patient population and in a different laboratory would arrive at the claimed invention. In response, Applicants assert that Imbert-Bismut *et al.* do not teach or suggest the use of the specific combination of markers recited in amended claim 54. In particular, Imbert-Bismut *et al.* teach that α2-MG, α2-globulin, gamma globulin, apolipoprotein A1, gamma glutamyltranspeptidase, and total bilirubin are the most informative markers for diagnosing liver fibrosis, but simply fail to teach or suggest the ***combined use of α2-MG and HA*** as is presently claimed for diagnosing liver fibrosis as set forth in amended claim 54. As a result, one skilled in the art would not have been motivated to modify the analysis of the 5 or 6 marker panels taught by Imbert-Bismut *et al.* to arrive at the claimed invention because Imbert-Bismut *et al.* do not teach or suggest the use of α2-MG in combination with HA for diagnosing liver fibrosis. Further, one skilled in the art would not have had any reasonable expectation that a method for diagnosing liver fibrosis using a combination of α2-MG and HA would be successful based upon the teaching of Imbert-Bismut *et al.* As such, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103(a) rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
JS:jch/sea
60350345 v1